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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,626	07/07/2005	Haruo Hanawa	0760-0347PUS1	8303

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	05/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 05/01/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/541,626	HANAWA, HARUO	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *7-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :7/7/05, 10/7/05, 11/6/06, and 1/22/07.

DETAILED ACTION

An amendment was received and entered on 3/26/07. Applicant's election with traverse of group 1 is acknowledged. Traversal is on the grounds that the claims of group 1 constitute a common technical feature that links all three groups of claims. This is not found persuasive because Applicant has not specifically identified the special technical feature allegedly constituted by the claims of group 1, and has not pointed out any error in the Examiner's determination of a technical feature linking the inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/26/07.

Information Disclosure Statement

Information disclosure statements were received on 7/7/05, 10/7/05, 11/6/06, and 1/22/07. All references were considered. All references n the IDS of 11/6/06 were lined through because they duplicate references on the IDS of 7/7/05.

Claim Objections

Claims 5 and 6 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent

claim. See MPEP § 608.01(n). Accordingly, the claims 5 and 6 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 are indefinite because it is unclear what is intended by "glucagon C-terminal side 19-29 amino acid peptide region". In particular, it is unclear what is the effect of the term "region" on the breadth of the claims. It is unclear if the claims exclude from the fusion protein glucagon residues 1-18, or if these residues may be included in addition to residues 19-29.

Claims 1-4 are indefinite because claim 1 recites "the body" without antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a vector with the intended use of "gene therapy". The claims do not limit the disease or disorder intended to be treated, and do not recite any therapeutic gene comprised by the vector.

This rejection can be overcome by deleting the intended use "for gene therapy" from the claims.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This

idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. Rosenberg et al (Science 287 :1751, 2000) stated that "[a}t present the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical trials a decade ago, gene therapy's leading proponents have given the field a positive "spin" that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." See first full paragraph. Juengst (BMJ 326: 1410, 2003) indicated that the effects of gene therapy on cells are often multiple and unpredictable. See title and last sentence of first full paragraph of column 2. In summary, it is clear that gene therapy is considered highly experimental area of research at this time, and researchers acknowledge that demonstrable progress to date has fallen short of initial expectations due to inadequate delivery and expression systems, and the unpredictable and pleiotropic effects of gene insertion and/or expression.

Guidance and Examples in the Specification

The instant specification is directed to a vector that allows detection and quantification of gene expression in a host. The specification does not address the art-recognized difficulties with gene delivery or expression, and there is no evidence that these have been overcome by the claimed invention. The specification teaches a three working examples of gene therapy. In one, CTLA4 is expressed in a heart transplant

model, and CTLA4 expression correlates negatively with transplant rejection. However, the sample size is small (15 animals divided among experiment and control groups) so the significance of the results is unclear. The other two examples involve treatment of myocarditis by administration of vectors of the invention encoding IL-13 or an IL-1/igG Fc fusion. The specification reports positive results in this model, but does not report the sample size, so the significance of the results is unknown. In any event, the intended use of the vector is not limited to any particular gene therapy, so 3 successful examples would not be enabling of the entire scope as claimed in view of the state of the art as discussed above.

Amount of Experimentation Required

Because the specification provides no guidance or working examples as to how to overcome the art-recognized barriers to the practice of gene therapy in general, particularly in view of the breadth of diseases and subject organisms encompassed by the claims, one of skill in the art could not practice the invention without undue experimentation. This rejection can be overcome by deleting the intended use "for gene therapy" from the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Biotech. Bioeng. 69(4): 418-428, 2000) in view of Conrad et al (J. Biol. Chem. 264(29): 17368-17373, 1989).

Kim taught that glucagon, including residues 19-29, can serve as a binding partner for affinity chromatographic purification of recombinantly-expressed fusion proteins. Kim exemplified a prokaryotic expression vector encoding a fusion of glucagon to the N-terminus of IL-2, and purification of the expressed fusion protein on an affinity column comprising a glucagon receptor. The protein of interest can be separated from the glucagon purification tag by enterokinase cleavage. See abstract; Fig. 1 on page 420; Affinity Column Chromatography (bridging columns 1 and 2 on page 421; paragraph bridging pages 424 and 426; Fig. 5 on page 425; and paragraph bridging pages 427 and 428.

Kim did not teach a mammalian expression vector.

Conrad taught mammalian expression vectors encoding IL-2, as well as expression of IL-2 in mammalian cells, and subsequent purification by multiple chromatographic steps taking 3 days. See abstract; page 17368, column 1, lines 1-10; and page 17370, column 2, "Purification of recombinant human IL-2".

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the purification method of Conrad by expressing IL-2 as a fusion to glucagon, as taught by Kim. One would have been motivated to do so because the method of Kim allows a single step purification of the fusion protein (see Affinity Column

Chromatography (bridging columns 1 and 2 on page 421), and so is much simpler. One of ordinary skill appreciates that mature, glycosylated IL-2 can be separated easily by enterokinase cleavage and repassage through the affinity column to remove the cleaved glucagon affinity tag. Thus the invention as a whole was prima facie obvious.

It is noted that the preamble of claim 1 states "A vector for gene therapy". This limitation is considered to be met because the vector of Conrad, as modified by Kim, meets all of the structural limitations of the claims. Accordingly, the functional limitations are considered to be met as well. Thus the invention as a whole was prima facie obvious.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Biotech. Bioeng. 69(4): 418-428, 2000) in view of Conrad et al (J. Biol. Chem. 264(29): 17368-17373, 1989) and Saunders et al (US 5486599).

The teachings of Kim and Conrad are discussed above. These references render obvious a mammalian expression vector encoding a fusion protein comprising IL-2 with a glucagon purification tag attached to the N-terminus of IL-2.

These references do not teach a fusion protein with glucagon attached to the C-terminus of IL-2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to construct a fusion protein comprising a glucagon purification tag at either the N- or C-termini of IL-2, or any other protein of interest. The terminus at which the fusion is made is simply a matter of design choice, as evidenced by Saunders who

indicated that that affinity purification tags can be placed either terminus. See column 26, lines 33-41. Thus the invention as a whole was prima facie obvious.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Biotech. Bioeng. 69(4): 418-428, 2000) in view of Dorai et al (BIO/TECHNOLOGY 12: 890-897, 1994).

Kim taught that glucagon, including residues 19-29, can serve as a binding partner for affinity chromatographic purification of recombinantly-expressed fusion proteins. Kim exemplified a prokaryotic expression vector encoding a fusion of glucagon to the N-terminus of human IL-2, and purification of the expressed fusion protein on an affinity column comprising a glucagon receptor. The protein of interest can be separated from the glucagon purification tag by enterokinase cleavage. See abstract; Fig. 1 on page 420; Affinity Column Chromatography (bridging columns 1 and 2 on page 421; paragraph bridging pages 424 and 426; Fig. 5 on page 425; and paragraph bridging pages 427 and 428.

Kim did not teach a mammalian expression vector encoding a fusion protein.

Dorai taught mammalian expression vectors encoding single-chain Fv antibody proteins with C-terminal fusions to affinity purification tags such as the B domain of protein A (FB protein), S-peptide, and hexa-histidine. See abstract; and page 894, column 1, first paragraph through column 2, first full paragraph; paragraph bridging pages 896 and 897; and first full paragraph on page 897.

With regard to claims 1 and 2 alone, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the glucagon affinity purification tag of Kim for any of the purification tags of Dorai. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). This substitution would result in a mammalian expression vector comprising a nucleic acid encoding a fusion protein comprising glucagon at the C-terminus. It is noted that the preamble of claim 1 states "A vector for gene therapy". This limitation is considered to be met because the vector of Dorai, as modified by Kim, meets all of the structural limitations of the claims. Accordingly, the functional limitations are considered to be met as well.

Further, in consideration of claims 1-4, the references can be combined as follows. It would have been obvious to one of ordinary skill in the art at the time of the invention to express the IL-2/glucagon fusion protein of Kim from the mammalian expression vector of Dorai in the mammalian cells of Dorai. One would have been motivated to do so because human IL-2 is a glycoprotein, and one of ordinary skill appreciates that prokaryotes, including the E.coli expression host of Kim, do not support

polypeptide glycosylation. Thus in order to express a more authentic, glycosylated form of IL-2, one of ordinary skill would be motivated to use a mammalian expression vector and host, as taught by Dorai. In view of the combined teachings of Kim and Dorai regarding the N- or C-terminal positioning of the purification tag, it would have been obvious to one of ordinary skill in the art at the time of the invention to place the purification tag at either terminus of the protein of interest.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635